

5 protein of *A. terreus* (SEQ ID NO:91) are identified by the
invention described herein. Mutations at residues 31, 41,
52, 73, 101, 111, 133, 141, 153, 281, 367, and 389 of the
wild-type *lovE* protein of *A. terreus* have been identified
as being critical for the improvement of *lovE* regulator
10 protein function. Those mutations include: F31L, Q41K,
Q41R, T52I, T52N, C73R, P101S, P101Q, V111I, S133L, E141V,
E141K, C153Y, C153R, T281A, N367I, N367Y, P389S and P389L.
Each mutation, therefore, represents a change of one
conservative class of amino acids for another. For
15 example, the mutation F31L represents a change from a
Group 6 amino acid residue to a Group 2 amino acid residue
at position 31 of the wild-type, *lovE* regulator protein.

Thus, by way of non-limiting example, regulator
proteins of this aspect of the invention include at least
20 one of the following mutations: (1) a Group 6 amino acid
residue mutated to a Group 2 amino acid residue at
position 31, for example, the mutation represented by
F31L; (2) a Group 3 amino acid residue mutated to a Group 5
amino acid residue at position 41, for example, the
25 mutation represented by Q41K or Q41R; (3) a Group 4 amino
acid residue mutated to a Group 2 amino acid residue at
position 52, for example, the mutation represented by
T52I; (4) a Group 4 amino acid residue mutated to a Group
3 amino acid residue at position 52, for example, the
30 mutation represented by T52N; (5) a Group 4 amino acid
residue mutated to a Group 5 amino acid residue at
position 73, for example, the mutation represented by
C73R; (6) a Group 1 amino acid residue mutated to a Group
4 amino acid residue at position 101, for example, the
35 mutation represented by P101S; (7) a Group 1 amino acid
residue mutated to a Group 3 amino acid residue at
position 101, for example, the mutation represented by
P101Q; (8) a valine amino acid residue mutated to another
Group 2 amino acid residue at position 111, for example,
40 the mutation represented by V111I; (9) a Group 4 amino
acid residue mutated to a Group 2 amino acid residue at
position 133, for example, the mutation represented by
S133L; (10) a Group 3 amino acid residue mutated to a

5 Group 2 amino acid residue at position 141, for example,
the mutation represented by E141V; (11) a Group 3 amino
acid residue mutated to a Group 5 amino acid residue at
position 141, for example, the mutation represented by
E141K; (12) a Group 4 amino acid residue mutated to Group
10 6 amino acid residue at position 153, for example, the
mutation represented by C153Y; (13) a Group 4 amino acid
residue mutated to a Group 5 amino acid residue at
position 153, for example, the mutation represented by
C153R; (14) a Group 4 amino acid residue mutated to a
15 Group 1 amino acid residue at position 281, for example,
the mutation represented by T281A; (15) a Group 3 amino
acid residue mutated to a Group 2 amino acid residue at
position 367, for example, the mutation represented by
N367I; (16) a Group 3 amino acid residue mutated to a
20 Group 6 amino acid residue at position 367, for example,
the mutation represented by N367Y; (17) a Group 1 amino
acid residue mutated to Group 4 amino acid residue at
position 389, for example, the mutation represented by
P389S; and/or (18) a Group 1 amino acid residue mutated to
25 a Group 2 amino acid residue at position 389, for example,
the mutation represented by P389L.

In other embodiments of the first aspect, the
invention provides a variant of the lovE regulator protein
with at least two, or at least three, or at least four, or
30 at least five, or at least six, or at least seven, or at
least eight, or at least nine, or at least ten, or at
least eleven, or at least twelve, or at least thirteen, or
at least fourteen, or at least fifteen, or at least
sixteen, or at least seventeen, or at least eighteen of
35 the above described specific mutations.

In other embodiments of the first aspect, the
invention provides an isolated lovE variant regulator
protein having the sequence of SEQ ID NO:41, SEQ ID NO:42,
SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46,
40 SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50,
SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54,
SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58,

5 SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62,
SEQ ID NO:63, SEQ ID NO:64, or SEQ ID NO:65.

In a second aspect, the invention provides a nucleic
acid molecule encoding a variant regulator protein of
secondary metabolite production of the first aspect of the
10 invention. As used herein, the terms "nucleic acid" or
"nucleic acid molecule" refer to a deoxyribonucleotide or
ribonucleotide polymer in either single-or double-stranded
form, and unless otherwise limited, would encompass
analogs of natural nucleotides that can function in a
15 similar manner as the naturally occurring nucleotide.

In one embodiment of the second aspect, the invention
provides a nucleic acid molecule encoding a variant
protein of the lovE regulator protein of the first aspect
of the invention.

20 By way of non-limiting example, the invention
provides a nucleic acid molecule encoding a lovE variant
regulator protein having the sequence of SEQ ID NO:66, SEQ
ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID
NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID
25 NO:75, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:79, SEQ ID
NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID
NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, or SEQ ID
NO:90.

Poor transformation efficiency and the lack of
30 efficient selection systems frequently precludes the
screening of large numbers of variant regulator proteins
of secondary metabolites in the organism from which the
regulator protein is isolated. For example, there are
currently certain technical obstacles to the successful
35 screening of large numbers of variant regulator proteins
in the fungus *A. terreus*, an organism that produces the
secondary metabolite lovastatin.

The invention described herein takes advantage of the
genetically tractable and experimentally amenable organism
40 *Saccharomyces cerevisiae* for screening large numbers of
variant regulator proteins of secondary metabolite
production. Techniques common to the field of molecular
biology are well developed in *S. cerevisiae*, and large